TESTOSTERONE AND THE HEART

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Abstract

Testosterone (T) has a number of important effects on the cardiovascular system. In men, T levels begin to decrease after age 40, and this decrease has been associated with an increase in all-cause mortality and cardiovascular (CV) risk. Low T levels in men may increase their risk of developing coronary artery disease (CAD), metabolic syndrome, and type 2 diabetes. Reduced T levels in men with congestive heart failure (CHF) portends a poor prognosis and is associated with increased mortality. Studies have reported a reduced CV risk with higher endogenous T concentration, improvement of known CV risk factors with T therapy, and reduced mortality in T-deficient men who underwent T replacement therapy versus untreated men. Testosterone replacement therapy (TRT) has been shown to improve myocardial ischemia in men with CAD, improve exercise capacity in patients with CHF, and improve serum glucose levels, HbA1c, and insulin resistance in men with diabetes and prediabetes. There are no large long-term, placebo-controlled, randomized clinical trials to provide definitive conclusions about TRT and CV risk. However, there currently is no credible evidence that T therapy increases CV risk and substantial evidence that it does not. In fact, existing data suggests that T therapy may offer CV benefits to men.

The Endocrinology of Testosterone

Testosterone (T) is the principal male sex hormone, secreted primarily by the testes and transported in the blood by the carrier protein, sex-hormone binding globulin (SHBG). Only 1% to 2% of testosterone circulates in blood as unbound "free" testosterone, but this fraction exhibits the most potent biological activity. Dihydrotestosterone (DHT), the most biologically active androgen, is synthesized from testosterone by 5α-reductase and exerts its effects via a family of androgen receptors. Some biological effects of testosterone may result from its aromatization to estradiol and subsequent interaction with the estrogen receptor. In addition to developing primary and secondary sex characteristics, androgens have diverse anabolic functions such as increasing muscle mass and bone density.[1] Testosterone has also demonstrated a number of important effects on the cardiovascular system. In men, T levels begin to decrease after age 40, and this decrease has been associated with an increase in all-cause mortality and cardiovascular risk.[2,3] However, whether low T causes negative cardiovascular events or is simply associated with them has yet to be determined.[4] This review highlights the evidence underlying the major interrelationships between androgens and the cardiovascular system.

Testosterone Actions on Cardiovascular Cells

Testosterone and the more potent DHT bind to cytoplasmic androgen receptors (AR) that are chaperoned by heat shock proteins. Once bound, the DHT-AR complex migrates to the nucleus, dimerizes with another DHT-AR complex, associates with coactivator proteins, and transactivates a family of genes with androgen response elements that alter myocardial and vascular cell behavior.[1] Evidence also supports a direct rapid membrane effect of T on G-protein-coupled receptors, with an increase in inositol trisphosphate and diacylglycerol and subsequent alterations in cytoplasmic calcium and potassium channel activity.[5]

Cardiovascular Risk in Testosterone Deficiency

Definition

Testosterone deficiency (TD) is a well-established major medical condition that negatively impacts male sexuality, general health, and quality of life. Symptoms include decreased libido, erectile dysfunction, decreased energy, depressed mood, irritability, and decreased sense of well-being. In the correct clinical setting, the diagnosis of TD is usually confirmed by low serum concentrations of total T (e.g., < 200 ng/mL) drawn in the early morning. However, there is no specific value that reliably distinguishes men who experience signs and symptoms of TD from those who do not nor those who will likely respond to treatment. Interpretation of total T concentrations is confounded by variation between individuals, variation in serum SHBG, and variation in androgen sensitivity.[6] Furthermore, considerable controversy has arisen regarding the accuracy of currently available commercial testosterone assays, especially those showing T levels at the lower end of the "normal" range.[4] Free testosterone level may be a more reliable indicator of androgen status, but more studies are needed to confirm this. The prevalence of symptomatic TD ranges from 2.1% to 12.8% in middle-aged to older men, with an incidence of 12 new cases/1000 person-years in the United States and Europe. Populations at high risk for TD include men with CHF, type 2 diabetes, obesity, chronic obstructive pulmonary disorder, HIV, and chronic opioid use.[7]

Overall and Cardiovascular Mortality in Testosterone Deficiency

Low T levels are also associated with chronic medical conditions such as metabolic syndrome, diabetes, dyslipidemia, hypertension, renal failure, frailty, malignancy, and cardiovascular (CV) events. Several meta-analyses and systematic reviews have clearly associated TD with increased CV disease and mortality. Ruige et al. found that higher T levels were associated with a decreased risk for CV events in men > 70 years (HR of 0.84; 95% CI, 0.76–0.92) but not in younger men (HR of 1.01; 95% CI, 0.95-1.08).[8] In a meta-analysis by Araujo et al. that included 18 studies and more than 22,000 subjects, overall and CV mortality were related to T levels. The authors concluded that although there was considerable heterogeneity in the studies, low T levels were significantly associated with overall mortality and strongly ($P = .06$) associated with CV mortality.[9] Finally, Corona et al. screened 1,178 articles and found 70 in their meta-analysis that showed a clear association between

low T/high estradiol levels and CV disease.[10] Longitudinal studies demonstrated that overall mortality and CV mortality were highest in those with low T levels. Whether low T and increased mortality are simply covariates or a causal relationship remains to be proven.

Testosterone Deficiency and Coronary Artery Disease

In their 2013 review, Oskui and colleagues reported on evidence suggesting that men with lower levels of endogenous T are more likely to develop CAD during their lifetimes.[11] The severity of CAD has also been investigated as a function of serum T concentrations. Four studies have noted an inverse relationship between serum T levels and CAD severity,[6] with lower levels of serum T associated with more severe CAD and higher serum T levels associated with reduced severity.[11] However, these results should be interpreted with caution due to the relatively small sample size included in each study. Furthermore, the mechanism through which TD may exacerbate CAD is unknown. Additional research is needed to further evaluate the association between low T levels and CAD severity. Testosterone may have several types of action, including direct vasodilatory action, a direct effect on myocardial oxygen consumption, and membrane repolarization.[5,11]

Testosterone Deficiency and Congestive Heart Failure

Emerging evidence indicates that congestive heart failure (CHF) is more than just a syndrome affecting a failing heart. It is becoming clear that the pathophysiology of CHF involves other pathways as well, including the skeletal muscles and the endocrine system. Jankowska et al. studied 208 men with CHF and 366 healthy male controls. Low T levels were found in all NYHA classes of heart failure.[12] It has also been shown that reduced T levels in men with CHF portends a poor prognosis and is associated with increased mortality.[13]

Testosterone Deficiency and Dyslipidemia

The evidence regarding the association between baseline T levels and lipid subfractions is conflicting; therefore, there is no clear consensus among the numerous authors who have investigated this association. No definitive statement can be made regarding the effects of testosterone replacement therapy on the levels of either LDL or HDL cholesterol.[11]

Testosterone Deficiency and Metabolic Syndrome

Metabolic syndrome (MetS) has been shown to have a close relationship with TD. In a meta-analysis of cross-sectional and prospective observational studies, Brand et al. found an inverse relationship between total T, free T, and SHBG, respectively, and MetS (OR per quartile decrease = 1.7; 95% CI, 1.63-1.77). The association varied across the individual components of MetS and was strongest with hypertriglyceridemia, abdominal obesity, and hyperglycemia.[14] It has been well established that men with type 2 diabetes have lower levels of T compared to men without diabetes.[11] Population-based studies have revealed that men with the lowest quartile of endogenous serum T concentrations are at double the risk of developing type 2 diabetes and MetS.[6]

Impact of Testosterone Replacement Therapy

Overall Mortality in Testosterone Replacement Therapy

Hypogonadal men have more fat and less muscle. The Hypogonadism in Males study compared 836 hypogonadal men with 1,326 eugonadal men. The mean body mass index (BMI) for hypogonadal men was found to be 31.5 compared to 28.5 for eugonadal men. The authors also verified that the odds ratio for having hypogonadism was significantly higher in obese men, and there was a statistically significant negative correlation between total T level and BMI.[15] Testosterone replacement therapy (TRT) has been shown to decrease fat mass. In their meta-analysis, Corona et al. demonstrated that TRT led to a decrease of 2.19% in fat mass.[16]

There are no large long-term, placebo-controlled, randomized clinical trials to provide definitive conclusions about TRT and CV risk. However, there is a significant amount of literature from the past several decades that provides valuable information. Many studies have indicated that low serum T concentrations are associated with increased CV risk and mortality and that TRT may have clinically relevant CV benefits.[6]

Two recent observational studies reported increased CV risks in men who received testosterone prescriptions.[17,18] Although they gained a significant amount of media attention, neither study provided credible evidence of increased CV risk. In one study, Vigen et al. made an official correction for misreporting their primary results, which actually showed a lower percentage of adverse CV events in the T-treated group compared to untreated men.[19] In the other study, Finkle et al. had no control group, so it is unknown whether CV events differed between treated and untreated men with TD.[19] The U.S. Food and Drug Administration (FDA) reviewed the CV safety of T products shortly after publication of these articles. In its assessment of CV risks and T therapy, the FDA identified a total of only 4 studies suggesting an increased risk, yet none provided solid evidence to support this. By comparison, more than 100 studies have reported reduced CV risk with higher endogenous T concentration, improvement of known CV risk factors with T therapy, and reduced mortality in T-deficient men who underwent TRT versus untreated men.[19] Two recent studies in men who received TRT found reduced CV events in those whose follow-up T level normalized compared to men whose T concentration remained low.[20,21] Another large observational study noted that T therapy was associated with reduced risk of myocardial infarction in men in the highest risk category.[22] A recently published meta-analysis of 75 placebo-controlled studies, the largest to date, found no evidence of increased CV risk with T therapy and clear evidence of improved metabolic profiles.[23] An international expert consensus regarding testosterone deficiency and treatment, published in the July 2016 *Mayo Clinic Proceedings*, concluded: "There is no credible evidence at this time that T therapy increases CV risk and substantial evidence that it does not. Indeed, there is a strong signal that T therapy may offer CV benefits to men."[19]

Coronary Artery Disease and Myocardial Infarction

Three recent randomized, placebo-controlled trials demonstrated that administration of T improves myocardial ischemia in men with CAD. All three found that in men with CAD, testosterone prolongs the time to exercise-induced ST-segment depression as measured on treadmill stress testing.[24-26] Testosterone has been reported to have direct vasodilatory effects on coronary arteries in men with CAD.[26]

Congestive Heart Failure

Testosterone replacement therapy has been shown to significantly improve exercise capacity without affecting left ventricular ejection fraction (LVEF). Given emerging evidence from basic-science models, it is reasonable to assume that TRT positively affects the exercise capacity of CHF patients via a peripheral mechanism, such as promoting increased type I muscle fiber proliferation.[27] Four authors have investigated the effects of TRT on exercise capacity in

men with CHF. Toma et al. performed a meta-analysis of these studies and discovered that there was a net pooled improvement of 0.52 standard deviations in exercise capacity among those who received TRT. The meta-analysis revealed that patients treated with T experienced a 16.7% increase (equivalent to ~ 54 m) in the 6-minute walk test, a 15.9% increase in the isometric walk test, and a 22.7% increase in peak VO_2. All four studies included in this meta-analysis evaluated the effects of TRT on LVEF as well. Although T was shown to significantly improve exercise capacity, none of the studies found a significant change in LVEF, although NYHA class was shown to improve in two of the studies. Of the patients in the TRT group, 35% (20 of 57) experienced an improvement of ≥ 1 NYHA class in their functional capacity compared to only 9.8% of patients in the placebo group (5 of 51). No significant adverse CV events were noted.[28] Further studies are needed to evaluate the clinical effects of TRT in CHF, but testosterone appears to be a promising therapeutic option for patients with CHF. Thus, a large clinical trial would be warranted to determine the value of TRT in this patient group.

Metabolic Syndrome and Diabetes

Studies indicate that TRT can improve MetS and diabetes by decreasing serum glucose levels, HbA1c, and insulin resistance in men with diabetes and prediabetes.[6] Four studies in hypogonadal men with MetS or diabetes showed that insulin resistance improved in men who received T therapy, and fasting glucose and HbA1c were improved in three of the four studies.[29-32] In patients with type 2 diabetes and TD, Dihndsa et al. demonstrated an increase in insulin sensitivity using a hyperglycemic-euglycemic clamp, an increase in lean body mass using dual energy x-ray absorptiometry, and a decrease in subcutaneous fat using magnetic resonance imaging. In this study, fat biopsies were also used to show that the expression of insulin-signaling genes (IR-ß, IRS-1, AKT-2, and GLUT 4) was lower in men with TD and diabetes. Treatment with T upregulated these genes, thereby providing a molecular explanation for observed clinical changes.[33]

Other Side Effects and Risks of Testosterone Replacement Therapy

Prostate Cancer

In 2005, Calof et al. published a meta-analysis of 19 randomized placebo-controlled trials that included 651 men who received TRT and 433 men who received placebo. They reported two major differences between the groups. The TRT group had a significantly greater incidence of all prostate-related adverse events, with a pooled odds ratio of 1.78 (95% CI, 1.07-2.95). Combined prostate events included all instances of prostate biopsies, prostate cancer, prostate-specific antigen (PSA) > 4 ng/mL or a 1.5-ng/mL increase in PSA during the study period, increased International Prostate Symptom Score, and acute urinary frequency. However, none of the individual prostate-related adverse events significantly differed between groups, including incident prostate cancer, which showed no difference between the TRT group and placebo.[34] In 2016, Boyle et al. reported results of a meta-analysis on prostate cancer in TRT trials. They concluded that TRT for hypogonadism does not appear to increase PSA or the risk of prostate cancer. The summary relative risk of prostate cancer in TRT patients was 0.87 (95% CI, 0.30-2.50).[35]

Polycythemia

Calof et al. also found a significant (> 50%) increase in hematocrit in the TRT group—the most common adverse effect noted in that group, with a pooled odds ratio of 3.69 (95% CI, 1.82- 7.51). Among the subjects with elevated hematocrit, there was only one incident of serious complication (cerebral hemorrhage).[34] The most recent meta-analysis examining the adverse effects of TRT was performed by Fernandez-Balsells et al. in 2010. The eligibility criteria for this analysis included all placebo-controlled studies that enrolled men (1) with low or low-normal testosterone levels, and (2) who received any testosterone formulation for ≥ 3 months. Similar to the previous reports, TRT resulted in a significant increase in hemoglobin levels.[36]

Thromboembolic Events

In a double-blinded, randomized, placebo-controlled trial of TRT in 46 men with CAD, no adverse change in coagulation factors was found.[37] In general, higher levels of T are not associated with an increased risk of venous thrombosis or pulmonary embolism.[38] Ramasamy et al. found no increase in thrombotic events in a cohort of hypogonadal men on TRT compared to a comparable group of men not on TRT, all of whom were followed for more than 3 years.[39]

Summary and Conclusions

It is clear that testosterone is an active hormone in many aspects of cardiovascular health, and TD is clearly associated with poor cardiovascular outcomes. However, the effect of TRT remains unclear at this time. The U.S. FDA recommends that all T supplements carry a warning that they may increase the risk of heart attack and stroke. Many authors of systematic reviews on the CV risks of TRT call for a large randomized multicenter trial on this issue. In a comprehensive overview of systematic reviews to date, Onasanya and colleagues from the Johns Hopkins School of Public Heath concluded that currently available data regarding an association between TRT and CV events are conflicted.[40] At this time, a detailed discussion with patients about the risks and benefits of TRT is essential until further data is available.

Key Points:

- There is no credible evidence at this time that testosterone therapy increases cardiovascular risk, but there is substantial evidence that it does not.
- Many studies have indicated that low serum T concentrations are associated with increased cardiovascular risk and mortality and that testosterone replacement therapy may have clinically relevant cardiovascular benefits.
- Studies have reported reduced CV risk with higher endogenous testosterone concentration, improvement of known CV risk factors with T therapy, and reduced mortality in testosterone-deficient men who underwent testosterone replacement therapy versus untreated men.
- Testosterone replacement therapy has been shown to:
  - improve myocardial ischemia in men with CAD
  - improve exercise capacity in men with CHF
  - improve serum glucose levels, HbA1c, and insulin resistance in men with diabetes and prediabetes

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords: testosterone, dihydrotestosterone, androgen, testosterone deficiency, testosterone replacement therapy

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